THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.

May 21, 1974

MEMORANDUM

TO: RCH, JHK, FWN

FROM: WUG

SUBJECT: Tests for Stress.

On May 14 and 15, Vernon Reilly of Pacific Northwest Research Center, visited CTR. He spoke about some studies that his associates had been doing on manifestations of stress. In a remote way they were a continuation of some studies of a former associate of mine. Reilly has for many years worked with lactic acid dehydrogenase, an enzyme that is produced by a virus that is carried by many transplanted tumors. The virus is also carried in mice and is apparently slightly stressful. Reilly has also developed a caging system that puts a minimum of stress on his mice.

Experiment 1. C3H mice. Group 1 with LDH in regular cages. Group 2 in regular cages. Group 3 in the stressless cages.

Results: Group 1 - 90%+ mammary cancers by 70 weeks.
Group 2 - 70%+ mammary cancers by 70 weeks.
Group 3 - 0% mammary cancers by 50 weeks when about 70% and 50% of Groups 1 & 2 respectively had cancers.
All mice had the mammary tumor agent.

Experiment 2. Mice produce reportedly corticosterome (cs) exclusively as the adrenal glucocorticoid. A Dr. Spakman(?) at PNR has developed a sensitive method of quantitating cs in 0.05 ml plasma. They found that when mice arrived in their laboratory the cs was always high but declined, reaching base line levels in 2 weeks. Interpretation: shipping of mice is stressful.

Observation 3. Blood for the cs determinations is drawn from the retro-orbital veins. If one routinely bleeds a cage of mice he obtains very erratic levels of cs. If one takes animals 1 to 10 all in the same cage, removing 1 mouse every 3 or 4 minutes, the cs levels in 1 will be low and there will be a progressive increase in the cs levels up to mouse 10. It takes 3 or 4 minutes for the stress to be manifest and it is additive. Actually, if 2 cages are side by side the mice in the second cage will be influenced.

Observation 4. Mice were stressed and their cs starts to rise within a few minutes and stays up for 3-6 hours. (There are diurnal rhythms.) Lagging about one hour, as I recall, the circulating T lymphocytes almost entirely disappear as indicated by the decreased lymphocyte counts. (I did not go into the way he determined they were T lymphocytes. They were determined by plaque formation on

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SRBC so apparently hemolytic. The thymus starts to decrease in size. There is a decrease in the number of plaque-forming lymphocytes as determined by lysis of sheep red blood cells. Stress determinations can be done in 1 hour by cs, a bit later by the lymphocyte counts, and later by the plaque method. Presumably all are measurements of a response to stress.

Reilly did not have data on the influence of the repetition of stress or adaptation. He had no data on the strain differences in the response to stress. He did know that the responses were greater at one part of the day than at another.

Some thoughts: Might it not be a good idea to compare the stress responses of the strains that are to be used on the smoking experiment? What is the relation of the AHH inducibility to stress responses? Corticoids are great inducers of some hepatic enzyme systems. Tyrosince transaminase is, I believe, one of them. What do the goat-cell plaque counts being done at Scripps show? If there are differences, could they be associated with cs levels? With diurnal rhythms? Much of this work has not been published and there is need for some confidentiality.

W.U.G.

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